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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,170	09/19/2006	Per Holm	20481/0206861-US0	1691
7278	7590	06/24/2009		
DARBY & DARBY P.C. P.O. BOX 770 Church Street Station New York, NY 10008-0770			EXAMINER BLAKELY III, NELSON CLARENCE	
			ART UNIT 1614	PAPER NUMBER
			MAIL DATE 06/24/2009	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/581,170	<b>Applicant(s)</b> HOLM ET AL.	
	<b>Examiner</b> NELSON C. BLAKELY III	<b>Art Unit</b> 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 31 March 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-43 and 46-56 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-43 and 46-56 is/are rejected.
- 7) ☒ Claim(s) 4,10,14,31-33,41-43 and 48 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>11/14/2008</u> . | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Application Status***

Claims 1-43 and 46-56 of the instant application are pending, and are presented for examination on their merits.

### ***Election/Restrictions***

Applicant's election of polyethylene glycol as the oily material, in the reply filed on 03/31/2009, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election **without traverse** (MPEP § 818.03(a)).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

### ***Priority***

Receipt is acknowledged of the certified copy of foreign application no. PA 2003 01785, filed 12/03/2003, submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

***Information Disclosure Statement***

The Information Disclosure Statement, filed 11/14/2008, is acknowledged and considered.

***Applicant's Amendment***

Applicant's Preliminary Amendment, filed 05/30/2006, wherein the priority information and claims 1-43 and 46-56 are amended, and claims 44, 45 and 57 are canceled, is acknowledged.

***Specification***

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to use of legal phraseology, "comprising" (line 1) and "comprises" (line 3).

Correction is required. See MPEP § 608.01(b).

The disclosure is objected to for the following informality:

The use of the trademark Danocrine® has been noted in this application on page 2, line 36, for example. A trademark should be capitalized wherever it appears and be accompanied by the generic terminology.

Additionally, there are multiple uses of other trademarks on pages 17, 20 and 32, for example.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

### ***Claim Objections***

Claims 4, 10, 14, 31-33, 41-43 and 48 are objected to for the following informalities:

With regard to instant claims 4 and 14, Applicant is encouraged to use the term "The" in lieu of "A" when referencing the dependent claims.

With regard to instant claims 31-33 and 42, Applicant is encouraged to insert a " (comma)" after the claim number, e.g., "The composition according to claim 1, wherein...".

With regard to instant claim 31, Applicant is encouraged to substitute the term “an” with “a” in the recitation “an pharmaceutically acceptable additive”, in lines 1 and 2. Additionally, Applicant is encouraged to insert the term "and" between the terms "suspending agents," and "absorption enhancing agents", in line 5.

With regard to instant claim 33, Applicant is encouraged to insert the term “is” between the terms “excipient” and “a silica acid”, in line 2.

With regard to instant claim 43, Applicant is encouraged to remove the “, (comma)” after the term “and”.

With regard to instant claim 40, Applicant is encouraged to replace the term “subsequent” with “subsequently”, in line 3, for the accuracy and precision of the claim language.

With regard to instant claim 48, Applicant is encouraged to remove the recitation “any of”, in line 1.

With regard to instant claims 10, 41 and 42, Applicant is encouraged to provide the literal translations of the abbreviated terms, e.g., MRT (mean residence time).

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 32, 33 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims recite the limitations, “analogue”, in reference to the claimed compound danazol (instant claim 8), and “derivative”, in reference to silica acid (instant claims 32, 33 and 41). Applicant has not described the claimed genus of “analogue” and “derivative” in a manner that would indicate Applicant was in possession of the full scope of this genus, or describe of what this genus is comprised. The instant specification, on page 4, lines 4-6, discloses that the term “danazol” encompasses any relevant derivative or analogue of danazol. Further, the specification, on page 14, lines 1-11, discloses suitable fillers, such as hydroxyethylcellulose, sodium carboxymethylcellulose and other cellulose derivatives, for example. This exemplification is not a definition that allows the Examiner, or one of ordinary skill in the art, to ascertain that Applicant was in possession of the full scope of this genus.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP § 2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, “not a mere wish or plan for obtaining the claimed chemical

invention.” *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office (“PTO”) Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.1 “Written Description” Requirement (“Guidelines”), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by “showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, “including, *inter alia*, “functional characteristics when coupled with a known or disclosed correlation between function and structure...” *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, Applicants have not described the genus of “analogue” and “derivative” in a manner that would allow one skilled in the art to immediately envisage the compounds contemplated for use. As such, the claims lack adequate written description for the claimed “analogue” and “derivative”.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4, 5, 7-9, 11-29, 35, 37, 38, 40, 49 and 51-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 2, 4, 5, 7, 9, 13-20, 22-29, 37, 38, 40, 49, 54 and 56, the phrase "(such as,) e.g." renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 5, 8, 9, 11, 12, 55 and 56 contain the trademark/trade name Danocrine®. Claim 35 contains multiple trademark/trade names for the silicon dioxide product, such as Zeofree® 5161A. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe danazol or silicon dioxide product and, accordingly, the identification/description is indefinite.

With regard to instant claims 5, 21 and 35, the recitations "(t=7 hours)", claim 5, "(paddle)", claim 21 and "(available from J.M. Huber, Hamina, Finland)", claim 35, render the claim(s) indefinite. The rejection is based on parenthetical subject matter.

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Confusingly, it is unclear to the Examiner, or one of ordinary skill in the art, at the time of the invention, whether or not a claim limitation is intended by the parenthetical subject matter. Applicant is encouraged to amend the claims for the accuracy and precision of the claim language.

With regard to instant claims 8, 9, 23-29, 55 and 56, the recitation “at (the) most about” is confusing. It is unclear to the Examiner, or one of ordinary skill in the art, to what degree the Applicant is seeking patent protection. “At (the) most” is a maxima encompassing all values below the claimed recitation. “About” encompasses a range centered on the claimed recitation. It is unclear as to whether “at (the) most” or “about” governs. Applicant is encouraged to amend the claim to clarify this confusion.

With regard to instant claims 13-20, 22 and 51-53, the recitation “at least about” is confusing. It is unclear to the Examiner, or one of ordinary skill in the art, to what degree the Applicant is seeking patent protection. “At least” is a minima encompassing all values above the claimed recitation. “About” encompasses a range centered on the claimed recitation. It is unclear as to whether “at least” or “about” governs. Applicant is encouraged to amend the claim to clarify this confusion.

With regard to instant claims 13-20, the recitation “within about” is confusing. It is unclear to the Examiner, or one of ordinary skill in the art, to what degree the Applicant is seeking patent protection. “Within” encompasses a range between two points. “About” encompasses a range centered on the claimed recitation. It is unclear as to whether “within” or “about” governs. Applicant is encouraged to amend the claim to clarify this confusion.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-41, 43 and 46-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adeyeye *et al.* (U.S. Patent Application Publication No.

2003/0083309A1), in view of Lerner *et al.* (International Publication No. WO03/082247A2) and Keller (U.S. Patent Application No. 2003/0003144A1), as evidenced by Galinsky *et al.* ["Basic Pharmacokinetics and Pharmacodynamics." in: Remington: The Science and Practice of Pharmacy (Baltimore, Lippincott Williams & Wilkins, 2006), p. 1171.].

With regard to instant claims 1-41, 43 and 46-56, Adeyeye *et al.* disclose, in reference claims 1-7 and 11, on page 5, a controlled release pharmaceutical composition comprising a water-soluble polydextrose, a drug, i.e., danazol, complexed with said water soluble polydextrose and a polymer, i.e., hydroxypropyl methylcellulose K15M (excipient; See also instant claim 41), for forming a polymer matrix having said drug complexed with said water-soluble polydextrose provide for a time release of said drug. In the instant excerpt, Adeyeye *et al.* further disclose wherein the pharmaceutical composition is a solid dosage form for buccal, or oral, administration (reference claim 11), as required by instant claims 1 and 48. Additionally, Adeyeye *et al.* disclose, in Figures 2-4, the *in vitro* dissolution profiles of various formulations of the controlled release pharmaceutical compositions of the instant invention, and the mean amount of plasma danazol concentration via the peroral route for Danocrine® capsules in comparison the peroral route (non-buccal; and buccal in Figure 4) for the danazol-SBE (sulfobutylether) 7 $\beta$ -CD (cyclodextrin) complex of the instant invention, in Figures 2 and 3, respectively (as required by instant claims 13-22, 55 and 56). In the instant excerpt, particularly Figures 3 and 4, Adeyeye *et al.* disclose wherein Danocrine® capsules comprise 200 mg danazol and the aforementioned complex comprises 50 mg (Figure 3)

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and 40 mg (Figure 4) danazol. Therefore, when compared to Danocrine®, the complex comprises approximately 25% ( $200 \text{ mg}/50 \text{ mg} = 0.25$  or 25%) and 20% danazol in Figures 3 and 4, respectively, as required by instant claims 8 and 9. On page 2, paragraph **[0023]**, Adeyeye *et al.* disclose, in particularly lines 13-15, that tablet dissolution was carried out by USP (United States Pharmacopeia) Type 2 method, wherein phosphate buffer pH 6.8 was used as a dissolution medium in all cases. Further, Adeyeye *et al.* disclose, in Example 3, paragraph **[0027]**, wherein the tablets were compressed on a Carver® press at a force of 6000 lb.f. (pound force) for 15 seconds (direct compression required by claims 46 and 47). In Example 4, pages 3 and 4, Adeyeye *et al.* disclose a study (results in Table 4 and Figures 3 and 4) wherein female beagle dogs were fasted (paragraph **[0029]**) and fed (paragraph **[0030]**), and subsequently administered the Danocrine® capsules, the aforementioned complex equivalent to 50 mg danazol and an intravenous dosing. In the instant excerpt, particularly Table 4, the pharmacokinetic evaluation of danazol in the plasma was considered, including the area under the curve (AUC),  $C_{\text{max}}$  (which would necessarily encompass  $C_{\text{diff}}$ ; See instant claim 5) and  $t_{\text{max}}$ , as required by instant claims 1-3, 5-7, 51-54. Further, in paragraph **[0032]**, page 4, Adeyeye *et al.* disclose that the area under the concentration time curve (AUC) from  $t=0$  to the time of the last blood sample was determined by the linear trapezoidal rule, which is well known by those skilled in the art.

Adeyeye *et al.* fail to disclose specifically wherein the composition comprising danazol exhibits a  $W_{50}$  that is about 2 hours or more, wherein the *in vitro* dissolution test

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employed a dissolution medium comprising a buffer at pH 7.5 (instant claims 16-22), wherein at the most about 10% of the active substance, i.e., danazol, is released within 2 hours, for example, wherein the dissolution medium has a pH of at the most about 5 (instant claims 23-28). However, it is not inventive to discover the optimum ranges or regimens by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) and MPEP §2144.05(II). In addition, Galinsky *et al.* recite in the left column of page 1171, lines 12-27 of text, that it is recognized that drug therapy may be optimized by designing regimens that account for the concentration of a drug, for example, to achieve a desired pharmacological response. Furthermore, because  $C_{max}$  was considered by Adeyeye *et al.* (See *supra*), a skilled artisan, at the time of the invention would have construed the value of  $W_{50}$ , which is the time where the plasma concentration is at least 50% of  $C_{max}$ , as required by instant claim 4. Additionally, Adeyeye *et al.* disclose wherein the phosphate buffer used comprised a pH 6.8 (See *supra*). Therefore, the determination of the optimum characterization of the composition would have been a matter well within the purview of one of ordinary skill in the art, at the time of the invention, through no more than routine experimentation.

Adeyeye *et al.* fail to disclose specifically wherein the composition comprising danazol reduces gastrointestinal side effects and reduces inter- and/or intra-individual variations compared to those of Danocrine®, in instant claims 11 and 12, respectively. However, an intended use of said composition, wherein the physical, structural, and functional components are identical or substantially similar, is not sufficient to patentably

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distinguish the claimed medicament over the prior art product containing identical physical and structural components [MPEP 2111.02 (II)].

Adeyeye *et al.* fail to disclose specifically wherein the one or more pharmaceutically acceptable excipients is silicon dioxide (instant claims 32-34), or wherein at least a part of danazol is present in the form of a solid dispersion including a molecular dispersion and a solid solution, wherein the solid dispersion is manufactured by dissolving at least a part of danazol in an organic solvent containing material suitable for forming solid dispersions and subsequently removing the organic solvent by evaporation, for example (instant claims 39-41). However, Lerner *et al.* disclose in, at least, reference claims 1-3, 6, 7 and 17, a drug delivery vehicle comprising a pharmaceutical carrier particle bearing microparticles of a drug, i.e., danazol (reference claim 3), deposited on the pharmaceutical carrier particle, i.e., microcrystalline cellulose (reference claims 6 and 7; a cellulose derivative as required by instant claim 41), from a solid solution of the drug in a sublimable carrier. In the instant excerpt, reference claims 17 and 20, Lerner *et al.* disclose an oral solid dosage form comprising a pharmaceutical composition, wherein the pharmaceutical composition additionally comprises at least one pharmaceutically acceptable excipient, e.g., glidants, flavorings and colorants (See page 8, lines 18 and 19; as required by instant claims 30 and 31). On page 8, lines 4-17, Lerner *et al.* disclose wherein binders, e.g., hydroxypropyl methylcellulose (instant claim 41), and disintegrants, e.g., colloidal silicon dioxide (instant claims 32-34), may be included. In Examples 2-6, pages 10-13, Lerner *et al.* disclose wherein menthol was melted with the desired drug, e.g., fenofibrate (Example 2) or danazol (See reference

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claim 3), until the drug dissolved, and microcrystalline cellulose (a cellulose derivative, as required by instant claim 41) was added to the melt, and the powder was transferred to a fluid bed dryer where the menthol (organic solvent) was removed by drying, or evaporation (See instant claims 39 and 40). Further, Lerner *et al.* disclose on page 6, lines 1-12, wherein the solid solutions of the reference invention may exist as a true homogeneous crystalline phase of the interstitial or substitutional type, composed of distinct chemical species occupying the lattice points at random, or they may be in a dispersion of discrete molecules or aggregates of molecules in the sublimable carrier (See instant claim 39). Lerner *et al.* disclose, on page 5, lines 1-9, that useful pharmaceutical carrier particles include particles, which may be non-pareil pellets, typically between about 0.1 mm and about 2 mm in diameter, as required by instant claim 29.

Lerner *et al.* fail to disclose specifically wherein the silicon dioxide product has properties corresponding to Zeofree® 5161A, for example, in instant claim 35; however, Lerner *et al.* does disclose colloidal silicon dioxide (See *supra*). Further, MPEP § 2112 I. recites that “[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer”. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Lerner *et al.* fail to disclose specifically wherein the composition, in the form of a particulate material, has a geometric weight mean diameter ( $d_{gw}$ ) of  $\geq 10 \mu m$  (instant claim 29); however, calculating the mean diameter of the log normal volume-size distribution, or  $d_{gw}$ , would have been a skill of an artisan at the time of the invention, especially given the consideration of pellet size, as disclosed by Lerner *et al.* (See *supra*). Furthermore, it is not inventive to discover the optimum ranges or regimens by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) and MPEP §2144.05(II). Therefore, the determination of the optimum characterization of the composition would have been a matter well within the purview of one of ordinary skill in the art, at the time of the invention, through no more than routine experimentation.

Adeyeye *et al.* fail to disclose specifically wherein said composition comprises an oily material with a concentration of about 5% w/w or more (instant claims 36-38), or wherein the concentration of the composition, in particulate form, is in the range of from about 5% to 100% w/w (instant claims 49 and 50). However, Keller discloses in, at least, reference claims 1 and 8-12, a formulation comprising danazol, along with nifedipine and dextromethorphan, and one or more PEG-lipids (polyethylene glycol) in a soft elastic gelatin capsule, or a two-piece hard shell gelatin capsule capable of tolerating liquid in its interior, wherein the danazol is in an amount between about %5 by weight to about 50% by weight (instant claims 49 and 50), and wherein the PEG-lipid is in an amount between about 50% by weight to about 95% by weight (instant claims 36-38). On page 1, paragraph [0004], Keller discloses wherein the oral dosage forms may

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be two-piece gelatin capsules, soft gelatin capsules and compressed and coated tablets.

Therefore, a skilled artisan would have envisaged the instantly claimed controlled-release composition comprising danazol, together with one or more pharmaceutically acceptable excipients, e.g., silicon dioxide, while taking the fundamental pharmacokinetics, such as AUC,  $C_{\max}$  and  $t_{\max}$ , into consideration, as disclosed by Adeyeye *et al.*, in view of Lerner *et al.* and Keller. One of ordinary skill in the art would have been motivated to combine the teachings of the aforementioned references when preparing a composition with increased bioavailability and a reduction in side effects of danazol associated with use of higher dosage amounts. It would have been obvious to one of ordinary skill in the art, at the time of the invention, because the combined teachings of the prior art are fairly suggestive of the claimed invention.

Accordingly, the instant invention, as claimed in claims 1-41, 43 and 46-56, is *prima facie* obvious over the combination of the aforementioned teachings.

Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adeyeye *et al.* (U.S. Patent Application Publication No. 2003/0083309A1), in view of Lerner *et al.* (International Publication No. WO03/082247A2) and Keller (U.S. Patent Application No. 2003/0003144A1), as evidenced by Galinsky *et al.* ["Basic Pharmacokinetics and Pharmacodynamics." in: Remington: The Science and Practice of Pharmacy (Baltimore, Lippincott Williams & Wilkins, 2006), p. 1171.], as applied to claims 1-41, 43

and 46-56 above, and further in view of Schüssele *et al.* (International Journal of Pharmaceutics, Vol. 257, Nos. 1-2, ages 301-304; 2003).

With regard to instant claim 42, the teachings of Adeyeye *et al.*, Lerner *et al.*, Keller and Galinsky *et al.* are recited *supra*.

Adeyeye *et al.* fail to disclose wherein the composition has an acceptable flowability as determined according to the method described in Ph.Eur. measuring the flow rate of the material out of a funnel with a nozzle diameter of 10.0 mm (instant claim 42). However, Schüssele *et al.* disclose, in the Abstract, flowabilities of commercially available, direct compression excipients examined according to the technical procedure described in the current European Pharmacopoeia (Ph.Eur.). On page 301, column 1, Schüssele *et al.* disclose wherein optimum flowability of powders is crucial in the manufacturing process of solid single dose preparations. In the instant excerpt, Schüssele *et al.* further disclose that the European Pharmacopoeia contains a test on “Flowability”, which examines the ability of a powder to flow vertically out of a funnel, wherein the results are expressed in units time per mass (e.g., seconds per 100 g sample; See page 302, second column, lines 5-16). In Table 2, page 303, Schüssele *et al.* disclose the results of Flowability measurements taken by the commercially available Sotax Powder Flow Tester FT 300, which introduces vibrations before and/or during the flow test in order to simulate the manufacturing process (See page 303, first column, second paragraph). In the instant excerpt, Schüssele *et al.* further disclose that a value of > 0.9 is regarded as having very good flowability.

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Therefore, when considering the varying densities of commonly used materials, which encompass both organic and inorganic substances, a skilled artisan, at the time of the invention, would have considered excipients with good flowability when preparing tablets obtained by direct compression. It would have been obvious to one of ordinary skill in the art, at the time of the invention, because the combined teachings of the prior art are fairly suggestive of the claimed invention.

Accordingly, the instant invention, as claimed in claim 42, is *prima facie* obvious over the combination of the aforementioned teachings.

### **Conclusion**

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NELSON C. BLAKELY III whose telephone number is (571) 270-3290. The examiner can normally be reached on Mon - Thurs, 7:00 am - 5:30 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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June 21, 2009

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